

# Treating the Periphery to Ameliorate Neurodegenerative Diseases

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**Abnormalities in the kynurenine pathway are associated with neurodegenerative disorders. Zwillig et al. (2011) show that inhibition of kynurenine 3-monooxygenase in the body's periphery leads to an increase in kynurenic acid, a neuroprotective compound, in the brain. This intervention ameliorates neurodegeneration in mouse models of Alzheimer's disease and Huntington's disease.**

One of the cellular pathways previously linked to neurodegenerative diseases, including Alzheimer's disease (AD) (Jacobson et al., 2005) and Huntington's disease (HD) (Crook and Housman, 2011), is the kynurenine pathway of tryptophan degradation (Figure 1; Stone and Darlington, 2002; Schwarcz, 2004), the most important route of tryptophan catabolism in humans. Two metabolites in this pathway are elevated in the blood and brains of AD and HD patients: quinolinic acid is associated with glutamate receptor excitotoxicity, and 3-hydroxykynurenine is associated with free radical generation. In contrast, the concentration of kynurenic acid, which is thought to be neuroprotective, is often decreased in AD and HD.

These observations serve as the basis of a new strategy of therapeutic intervention described in this issue of *Cell*. Zwillig et al. (2011) show that the sustained inhibition of kynurenine 3-monooxygenase, the enzyme catalyzing the conversion of kynurenine to 3-hydroxykynurenine, appears to reverse a number of cognitive and motor deficits measured in AD and HD mouse models. Inhibiting this enzyme has the effect of elevating neuroprotective kynurenic acid levels while decreasing the levels of neurotoxic quinolinic acid and 3-hydroxykynurenine.

There are two interesting twists to this story. Inhibition of peripheral kynurenine 3-monooxygenase gives rise to an increase in peripheral kynurenine, which is efficiently transported to the brain, where it is rapidly converted to the neuroprotective

metabolite kynurenic acid. Hence, the first twist is that inhibition of a peripheral enzyme translates into the elevation of a neuroprotective molecule in brain. Soluble enzyme inhibition in the periphery is a proven therapeutic strategy employed by the pharmaceutical industry to treat a spectrum of diseases.

The second twist to this story is that the synthesis of a new prodrug, referred to as JM6, gives rise to the sustained release of a previously characterized kynurenine 3-monooxygenase inhibitor, Ro 61-8048 (Doody et al., 2011). This prodrug approach was developed to overcome metabolic instability.

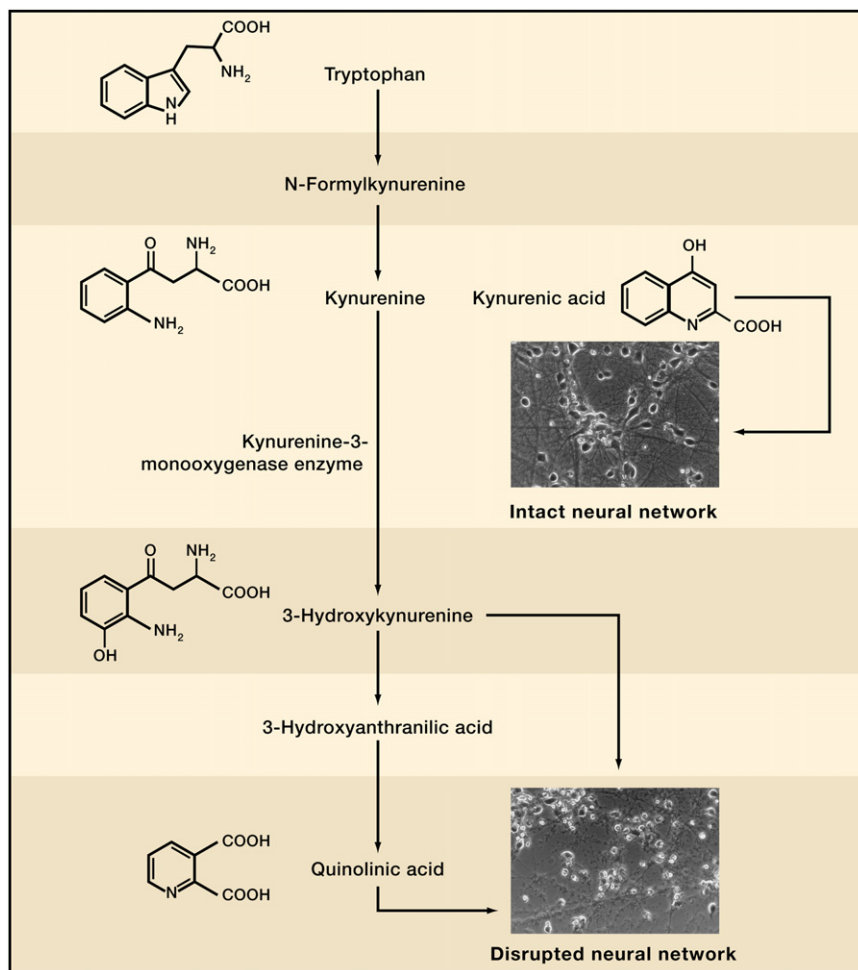
Further raising interest in the same metabolic pathway, Giorgini and colleagues (Campesan et al., 2011, recently published in *Current Biology*) provide persuasive genetic and pharmacological evidence that inhibition of kynurenine 3-monooxygenase, or tryptophan 2,3-dioxygenase, the most upstream tryptophan degrading enzyme, is neuroprotective in a fruit fly model of HD. This efficacy appears to be linked to an increase in the neuroprotective metabolite kynurenic acid relative to 3-hydroxykynurenine. Furthermore, these authors demonstrate that simply feeding kynurenic acid to HD model flies protects them from neurodegeneration, whereas feeding 3-hydroxykynurenine exacerbates cytotoxicity.

Though it is likely that multiple deficiencies act together to cause neurodegeneration and that mechanistically dis-

tinct drugs will ultimately be required to halt the progression of neurodegenerative diseases, the kynurenine 3-monooxygenase inhibition strategy is promising because it offers the potential to alleviate more than one neurodegenerative disease. This is particularly appealing because of the difficulty in conducting successful clinical trials in diseases like AD (Röver et al., 1997). Thus, an agent that proves useful in multiple maladies could be discovered by an initial trial in a disorder like Huntington's disease, wherein the cause—an autosomal dominant mutation in the huntingtin protein—is much better understood, and disease progression in placebo controls is better characterized.

Interestingly, JM6 and Ro 61-8048 do not enter the brain at appreciable concentrations. This finding could prove to be useful for maximizing clinical benefit and managing toxicity in combination therapies for the treatment of neurodegenerative disease. Because most current therapeutic approaches select compounds for preferential brain exposure, compounds that function by a peripheral mechanism may be desirable combination partners.

In transgenic mice overexpressing amyloid precursor protein, JM6 can improve behavioral endpoints in spatial memory assays and anxiety assays. That JM6 has no obvious effects on plaque size and number raises interesting questions that merit further investigation. For example, is there any intersection between kynurenine 3-monooxygenase inhibition and the amyloid cascade, say at the level



**Figure 1. The Kynurenine Pathway and Neurodegeneration**

The kynurenine pathway of tryptophan degradation is the most important route of tryptophan catabolism in humans. Some metabolites within this pathway are elevated in blood and in the brains of patients with Alzheimer's disease or Huntington's disease. Specifically, there are elevations in quinolinic acid, which is associated with glutamate receptor excitotoxicity, and 3-hydroxykynurenine, which is linked to free radical generation. In contrast, the concentration of kynurenic acid, thought to be neuroprotective, is decreased. *Drosophila* do not synthesize quinolinic acid, the final product of tryptophan degradation in the human kynurenine pathway. Photomicrographs are from Usui et al. (2009).

of A $\beta$  oligomers, or is this a completely independent mechanism? Does kynurenine 3-monooxygenase inhibition intersect with Tau pathology? What are the molecular mechanisms downstream of kynurenic acid elevation? Are the enhanced life span endpoints that are measured in HD

models also independent of huntingtin inclusions?

A number of questions defining the relationship between the drug's pharmacokinetics and pharmacodynamics remain to be elaborated. What is the minimal elevation in kynurenic acid that has thera-

peutic benefit? The authors have shown efficacy following chronic dosing for 4 months. How long does the inhibition of kynurenine 3-monooxygenase need to be sustained? Lastly, is this treatment approach prophylactic, or is it efficacious in animals that are already suffering from HD aggregates and the associated behavioral deficits?

These innovative studies and previous results suggest that decreasing the ratio of 3-hydroxykynurenine and quinolinic acid to kynurenic acid using small-molecule inhibitors could be used to treat AD and HD. As is often the case with new data that force us to re-evaluate what we know about disease progression and intervention, these studies also raise many new questions, in addition to providing hope to patients with these maladies.

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